Disclosure of Alzheimer's disease biomarker status in subjects with mild cognitive impairment

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DOI: https://doi.org/10.2217/bmm.12.58

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"*Future studies ... [will] improve the opportunities for an informed choice for Alzheimer's disease biomarker assessment and disclosure of the results.*"

KEYWORDS: Alzheimer's disease ■ CSF biomarkers ■ diagnostic disclosure ■ mild cognitive impairment

Biomarkers for Alzheimer's disease (AD) pathology now give the opportunity to diagnose AD in subjects with mild cognitive impairment (MCI). AD biomarker assessment in this population is currently not part of routine clinical care, but it is nevertheless performed with increasing frequency. This raises several practical and ethical issues. The disclosure of AD biomarker status may have a stronger impact on subjects with MCI than on demented subjects. In addition, AD biomarker scores may often be near the threshold for an abnormal score or may be conflicting with other AD biomarker scores because of the early disease stage. Moreover, the prognosis of MCI subjects with abnormal AD biomarkers remains uncertain for individual patients. In this editorial, we will comment on the interpretation of AD biomarker scores in subjects with MCI and present an approach to disclose them.

Current diagnostic work-up of subjects with MCI

MCI refers to objective cognitive impairment that is not severe enough to warrant a diagnosis of dementia. The diagnosis is based on a clinical examination including administration of rating scales or neuropsychological tests. MCI is a syndromal diagnosis that can be caused by somatic, psychiatric or neurological conditions. A total of 30–80% of subjects have AD as the underlying pathology depending on the definition of MCI and the age of the subject [1]. The diagnostic work-up of subjects with MCI typically consists of blood analysis and computed tomography or MRI in order to identify causes of MCI that may be treatable such as metabolic or vascular disorders. The majority of the patients with MCI are told that they have an increased risk for AD, and almost 90% are invited for follow-up [2].

Potential advantages & disadvantages of AD biomarker testing in subjects with MCI

The obvious advantage of AD biomarker analysis is that subjects can be informed on whether AD is the underlying cause of their impairments. This may reduce uncertainty compared with the situation in which subjects are told that MCI is associated with an increased risk for AD but that follow-up is needed to determine the outcome. Information on AD biomarker status will help MCI subjects and their relatives to understand the cause of the impairments and to anticipate the future [3]. It will also help clinicians to plan medical care.

There are also several disadvantages. The outcome of MCI subjects with abnormal AD biomarkers is uncertain: patients may become demented within 1 year or after 10 years [4]. There are no therapeutic implications as evidence-based treatment for MCI subjects with abnormal AD biomarkers is lacking. Information on the presence of AD biomarkers may cause stress to patients and the family and may have implications for health insurance or work.

Which AD biomarkers are available?

According to the amyloid cascade hypothesis, the primary event in AD is abnormal amyloid processing, which is then followed by neuronal injury. Biomarkers for AD can likewise be subdivided into markers for amyloid dysregulation and markers for neuronal injury. Research criteria for AD recommend decreased β-amyloid (Aβ)1–42 in cerebrospinal fluid (CSF) and increased binding of PET-amyloid tracers as markers of amyloid pathology and increased tau in CSF, hippocampal atrophy and hypoperfusion or hypometabolism as measured by PET or single-photon emission computed tomography imaging as markers for neuronal injury [5,6].

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Interpretation of AD biomarker scores

There are several general considerations for interpreting biomarker results. First, while AD biomarkers relate to AD pathology, our understanding of AD pathophysiology is incomplete. For example, the type of amyloid aggregation may vary and this may be reflected in biomarker scores [7]. Areas affected by neurodegeneration differ between patients and this also influences biomarker scores [8]. Moreover, diagnostic and prognostic accuracy vary with the position of biomarkers in the amyloid cascade [9]. Amyloid markers have a higher sensitivity for the diagnosis of AD in subjects with MCI than injury markers [4,9,10]. By contrast, injury markers have a better prognostic value than amyloid markers and can predict time to onset of dementia [9]. Finally, it is difficult to provide numeric data for prognosis to individual patients. Most studies have a follow-up of less than 3 years, and the few studies with a long-term follow-up need cross-validation. Studies on the outcome of borderline or conflicting biomarker scores are lacking.

Interpretation of abnormal test scores

Abnormal biomarker scores increase the likelihood for conversion to AD-type dementia within 3 years by a factor of 2–4 [11–14]. After an average follow-up of 9 years, approximately 90% of the subjects with a combination of abnormal Aβ1–42 and tau in CSF converted to AD-type dementia [4]. We found that 30% of the subjects with abnormal CSF Aβ1–42 and normal injury markers converted to AD-type dementia after 4 years compared with 80–90% of the subjects with abnormal CSF Aβ1–42 and one or more abnormal injury markers [15].

Interpretation of normal test scores

A normal biomarker score reduces the likelihood for progression to AD-type dementia within 3 years by a factor of 2–6 [11–14]. After an average follow-up of 9 years, however, approximately 20% of the subjects with a combination of normal Aβ1–42 and tau in CSF at baseline converted to AD-type dementia [4]. In another study, 15% of the subjects with both normal amyloid and injury markers converted to AD-type dementia after 5 years [16].

Interpretation of test scores near the cut-off point

Scores near the cut-off point are common. Our own unpublished data showed that 16% of the subjects with MCI had a CSF Aβ1–42 value 10% above or below the cut-off point for an abnormal score. A borderline score could mean that a subject is an early stage of the disease or it could result from inaccurate assay performance as the coefficient of variance for CSF Aβ1–42 or tau assays can be as large as 26% [17]. Borderline scores should therefore be interpreted together with results of other tests, and the coefficient of variance of the laboratory and biomarker or cognitive assessment may be repeated in 1 year.

Interpretation of conflicting test scores

Conflicting test scores are also common. Our own unpublished data showed that 60% of the subjects with MCI had conflicting scores for CSF Aβ1–42, CSF tau and hippocampal atrophy. Conflicting amyloid markers could result from differences between CSF and PET markers in their ability to detect specific types of amyloid aggregation [7]. Conflicting injury markers may indicate variability in disease expression [9]. Abnormal amyloid markers with normal injury markers may reflect early-stage AD or non-AD causes of MCI such as Lewy body dementia [18]. Abnormal injury markers with normal amyloid markers may suggest non-AD causes of MCI or an atypical presentation of AD. Again, results should be interpreted together with results of other tests, and biomarker or cognitive assessment may be repeated.

Shared decision-making & disclosure

Given the uncertainties presented above and the lack of treatment implications, careful counseling of the patient should be performed before and after biomarker testing. As an approach for this, we propose the shared decision-making (SDM) model. In general, SDM is a process by which a healthcare choice is made jointly by the doctor and the patient. SDM can be positioned as a 'middle ground' between paternalism (i.e., physicians make the decisions) and informed choice (i.e., patients make the decisions) as described by Makoul and Clayman [19]. It is crucial to give information on possible outcomes before biomarker testing, as this will facilitate the disclosure of the results. With regards to MCI diagnosis, SDM includes the explanation of the memory problems by the patient and the presentation of diagnostic options by the physician. Advantages and disadvantages of further diagnostic steps should be discussed considering the fact that doctors and patients may have different perspectives on the relative importance

and benefits of the assessment. The lack of treatment opportunities with early diagnosis needs to be discussed in particular. Clear arrangements about the sequence of diagnostic tests should be made. In agreement with the patient, a decision may be deferred to a later time if agreement is sought with family members or other professionals. SDM and disclosure can be applied stepwise:

- Initial exploration and clinical examination of subject. Discuss:
  - The worry about possible AD and dementia, and whether this is the information the patients wishes to obtain;
  - The diagnostic assessments to be performed (history, cognitive testing and neurological, psychiatric and physical examination).
- Additional diagnostic testing not specific for AD. In case cognitive disturbances fit the MCI criteria, discuss the performance of neuroimaging, blood tests and other tests to identify causes of MCI, other than AD.
- Assessment AD biomarkers. In case no other causes of MCI are detected, mention the possibility of performing AD-specific diagnostic tests. Discuss:
  - The risk of AD without biomarker assessment;
  - The change in prognosis after AD biomarker assessment (abnormal score: AD likely but time to dementia uncertain; normal score: AD unlikely, although not excluded);
  - The possibility of contradictory results or borderline scores;
  - The lack of treatment implications if tests are abnormal;
  - The possible negative effects for psychological well-being, health insurance or work;
  - The type of tests available and strengths and limitations of each test;
  - The alternative for AD biomarker testing ('wait and see').

  The decision to continue the diagnostic process is taken together with the patient.
- Disclosure of biomarker results. Discuss implications of normal, abnormal, borderline or conflicting biomarker scores.

Future studies on borderline and conflicting scores and studies with long-term follow-up will further facilitate SDM and improve the opportunities for an informed choice for AD biomarker assessment and disclosure of the results.

Financial & competing interests disclosure

The study was in part funded by Zon Mw (PJ Visser) as part of the BIOMARKAPD project in the frame of the European Joint Programming Initiative on Neurodegenerative Disorders (JPND). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1 Visser PJ, Kester A, Jolles J, Verhey F. Ten-year risk of dementia in subjects with mild cognitive impairment. *Neurology* 67(7), 1201–1207 (2006).

2 Roberts JS, Karlawish JH, Uhlmann WR, Petersen RC, Green RC. Mild cognitive impairment in clinical care: a survey of American Academy of Neurology members. *Neurology* 75(5), 425–431 (2010).

3 Porteri C, Galluzzi S, Geroldi C, Frisoni GB. Diagnosis disclosure of prodromal Alzheimer disease ethical analysis of two cases. *Can. J. Neurol. Sci.* 37(1), 67–75 (2010).

4 Buchhave P, Minthon L, Zetterberg H, Wallin AK, Blennow K, Hansson O. Cerebrospinal fluid levels of beta-amyloid 1–42, but not of tau, are fully changed already 5 to 10 years before the onset of Alzheimer dementia. *Arch. Gen. Psychiatry* 69(1), 98–106 (2012).

5 Albert MS, Dekosky ST, Dickson D *et al.* The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging and Alzheimer's Association workgroup. *Alzheimers Dement.* 7(3), 270–279 (2011).

6 Dubois B, Feldman HH, Jacova C *et al.* Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol.* 9(11), 1118–1127 (2010).

7 Scholl M, Wall A, Thordardottir S *et al.* Low PiB PET retention in presence of pathologic CSF biomarkers in Arctic APP mutation carriers. *Neurology* doi:WNL.0b013-e31825fdf18 (2012) (Epub ahead of print).

8 Migliaccio R, Agosta F, Rascovsky K *et al.* Clinical syndromes associated with posterior atrophy: early age at onset AD spectrum. *Neurology* 73(19), 1571–1578 (2009).

9 Van Rossum IA, Visser PJ, Knol DL *et al.* Injury markers but not amyloid markers are associated with rapid progression from mild cognitive impairment to dementia in Alzheimer's disease. *J. Alzheimers Dis.* 29(2), 319–327 (2012).

10 Vos S, Van Rossum I, Burns L *et al.* Test sequence of CSF and MRI biomarkers for prediction of AD in subjects with MCI. *Neurobiol. Aging* doi:0.1016/j.neurobiolaging.2011.12.017 (2012) (Epub ahead of print).

11 Van Rossum IA, Vos S, Handels R, Visser PJ. Biomarkers as predictors for conversion

from mild cognitive impairment to Alzheimer-type dementia: implications for trial design. *J. Alzheimers Dis.* 20(3), 881–891 (2010).

12 Zhang S, Han D, Tan X, Feng J, Guo Y, Ding Y. Diagnostic accuracy of ^{18}F-FDG and ^{11}C-PIB-PET for prediction of short-term conversion to Alzheimer's disease in subjects with mild cognitive impairment. *Int. Natl J. Clin. Prac.* 66(2), 185–198 (2012).

13 Yuan Y, Gu ZX, Wei WS. Fluorodeoxyglucose-positron-emission tomography, single-photon emission tomography, and structural MR imaging for prediction of rapid conversion to Alzheimer disease in patients with mild cognitive impairment: a meta-analysis. *AJNR Am. J. Neuroradiol.* 30(2), 404–410 (2009).

14 Visser PJ. Mild cognitive impairment. In: *Principles and Practice of Geriatric Medicine.* Sinclair A (Ed.). John Wiley & Sons, UK, 1095–1103 (2006).

15 Van Rossum IA, Vos S, Burns L *et al.* Injury markers predict cognitive decline in subjects with MCI and amyloid pathology. *Neurology* (2012) (In press).

16 Galluzzi S, Geroldi C, Ghidoni R *et al.* The new Alzheimer's criteria in a naturalistic series of patients with mild cognitive impairment. *J. Neurol.* 257(12), 2004–2014 (2010).

17 Mattsson N, Andreasson U, Persson S *et al.* The Alzheimer's Association external quality control program for cerebrospinal fluid biomarkers. *Alzheimers Dement.* 7(4), 386–395.e6 (2011).

18 Mollenhauer B, Bibl M, Wiltfang J *et al.* Total tau protein, phosphorylated tau (181p) protein, beta-amyloid(1–42), and beta-amyloid(1–40) in cerebrospinal fluid of patients with dementia with Lewy bodies. *Clin. Chem. Lab. Med.* 44(2), 192–195 (2006).

19 Makoul G, Clayman ML. An integrative model of shared decision making in medical encounters. *Patient Educ. Couns.* 60(3), 301–312 (2006).